
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Ann Allergy Asthma Immunol 000 (2021) 1–2

Contents lists available at ScienceDirect

Letters

# Delayed hypersensitivity to the Comirnaty coronavirus disease 2019 vaccine presenting with pneumonitis and rash

Clinical trials have supported the efficacy of vaccines for the prevention of coronavirus disease 2019(COVID-19) infection, and widespread vaccination is now seen as a cornerstone in preventing mortality.[1] Postapproval surveillance has however revealed rare but significant vaccine-associated complications, including thrombosis with thrombocytopenia syndrome after the adenovirus vector ChAdOX1-S and Janssen vaccines[2] and myocarditis with messenger RNA –based vaccines.[3] This has highlighted the importance of ongoing pharmacovigilance and prompt reporting of suspected vaccine-associated adverse events. Here, we present a case of inflammatory pneumonitis and fixed rash after a second dose of the BioNTech Comirnaty COVID-19 vaccine with delayed hypersensitivity seen on skin testing.

A 55-year-old woman presented to hospital 6 days after the second dose of the Comirnaty COVID-19 vaccine with malaise, fever, cough, and an abdominal rash. She had tolerated the first dose, 3 weeks before, with brief pain at the injection site but no other signs of reactogenicity.

The patient initially tolerated the second vaccination, but a large, fixed, confluent, erythematous, nontender rash emerged over her right lower abdomen 48 hours after the dose. Notably, there were no accompanying skin changes over the injection site. The rash remained in a fixed distribution thereafter and did not improve with oral antimicrobial therapy. At 4 days from vaccination, she then developed a persistent nonproductive cough accompanied by progressive dyspnea, rigors, nausea, and anorexia, which eventually prompted her presentation to hospital.

On presentation, the patient was hypoxic with oxygen saturation of 91% on room air and febrile at 39.6°C. Blood investigations revealed lymphopenia with a lymphocyte count of $0.4 \times 10^9$/L and markedly elevated inflammatory markers with C-reactive protein of 512 mg/L but no other significant organ dysfunction. Multifocal bilateral lung infiltrates were found on chest x-ray examination with confluent changes in the right lower lobe.

The patient was commenced on intravenous ceftriaxone and azithromycin for presumed community-acquired pneumonia but remained persistently febrile and hypoxic. A computed tomography scan of the chest on the second day of admission revealed bilateral, multifocal ground-glass changes with peribronchial thickening (Fig 1). Bronchoscopy was performed 2 days later with visible clear mucoid secretions, and atypical bronchial cells were found on cytology results. Microbiological investigation results on bronchial washings were negative, including Gram stain, bacterial and fungal culture, viral polymerase chain reaction, microscopy for acid-fast bacilli, and *Mycobacterium tuberculosis* polymerase chain reaction.

Given the lack of response to broad-spectrum antibiotics, a noninfective inflammatory pneumonitis related to vaccination was considered, particularly in light of the abdominal rash. On the third day of admission, prednisone 25 mg daily was added to ongoing antibiotics; within 24 hours, there was resolution of the fever, improvement in the patient's symptoms, and downtrend in inflammatory markers. Topical 0.1% methylprednisone ointment was applied to the abdominal rash, which resolved after several days. Results of skin histopathology, taken on the day of admission, subsequently revealed mixed dermatitis with perivascular eosinophils and negative direct immunofluorescence, consistent with a drug reaction.

The patient was discharged on the sixth day of admission and completed a further week of oral antibiotics and tapering prednisone with complete resolution of symptoms. Owing to the atypical cells on bronchoscopy sample cytology, a positron emission tomography scan was performed 1 month later, which revealed mild glucose avidity in the right middle lobe and lingula, consistent with resolving inflammation but no other pulmonary lesions. Skin prick and intradermal testing to the Comirnaty COVID-19 vaccine demonstrated no immediate reaction, but a large 38 × 45-mm intradermal reaction to the 1:10 dilution of the vaccine was seen at 48 hours, consistent with delayed hypersensitivity.

This case reveals a previously undescribed delayed hypersensitivity to the Comirnaty COVID-19 vaccine presenting with pneumonitis and a fixed rash. Although other causes for the patient's presentation were considered, the lack of microbiological findings on bronchial fluid and minimal response to antibiotic therapy supported an inflammatory rather than infective cause, and no evidence of malignancy was subsequently found. Although positive delayed skin testing reactions can indicate a normal cellular immune response to mRNA COVID-19 vaccines,[4] the profound intradermal reaction seen in our patient, in addition to morphologic similarities to the original rash and skin biopsy findings supported vaccine-related hypersensitivity.

Vaccine-related pneumonitis has been reported after influenza vaccination and is thought to occur due to immune-mediated lung injury with demonstrated vaccine dependent in vitro proliferation of lymphocytes.[5] Meanwhile, respiratory complications after other vaccines, including COVID-19 vaccines, are not well described. To date, there has been 1 report of pulmonary nodules after mRNA-1273 vaccination but these were not glucose avid on positron emission tomography and hence likely benign,[6] although a case of acute respiratory distress syndrome has been recently reported.[7]

**Disclosures:** The authors have no conflicts of interest to report.
**Funding:** The authors have no funding sources to report.

https://doi.org/10.1016/j.anai.2021.11.014

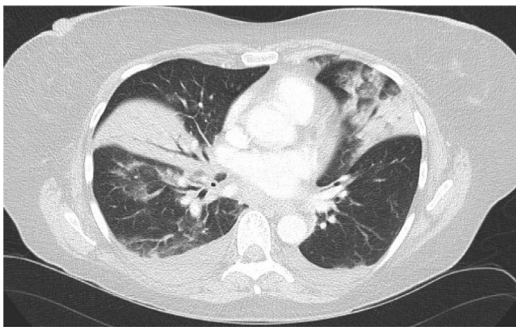

**Figure 1.** Computed tomography of the chest with axial view revealing diffuse ground-glass changes and peribronchial thickening on day 2 of the patient's hospital admission.

In contrast, delayed cutaneous local reactions at injection sites, coined "COVID arm," occur in up to 1% of recipients of mRNA COVID-19 vaccines.[8] Distant and generalized cutaneous reactions, including urticaria and morbilliform rashes, have also been described more recently. These typically occur up to 1 week after first dose or 2 to 4 days after the second dose, consistent with our patient's rash.[9]

Although vaccine-specific lymphocyte responses could not be performed in our patient, the intradermal testing and histopathologic features on skin biopsy support a possible T-cell–mediated mechanism. Unlike most of the delayed localized cutaneous reactions, our patient's presentation occurred after the second dose of the vaccine, but this phenomenon is well described in delayed drug hypersensitivity, and it is established that cellular responses are greater after the second vaccine dose.[10] The mechanism by which reactive lymphocytes may be generated remains unclear, but immediate and delayed skin testing to polyethylene glycol (PEG 3350), one of the excipients in the Comirnaty vaccine, was negative at several concentrations. This suggests that the process was possibly driven by other components, including the lipid-based nanoparticle carrier. We therefore recommended that our patient avoid all mRNA COVID-19 vaccines but can receive non–mRNA-based vaccines, when booster doses are required.

In summary, we describe a unique presentation of delayed hypersensitivity to the Comirnaty COVID-19 vaccine. This case adds to the growing evidence for rare delayed reactions to COVID-19 vaccines and highlights the importance of ongoing pharmacovigilance as the vaccine rollout continues.

Alex Stoyanov, MBBS (Hons), MSc[*]
Graeme Thompson, MBBS (Hons)[†,‡]
Monique Lee, MBBS (Hons)[*]
Connie Katelaris, MBBS, PhD[*,,‡]
[*] *Department of Clinical Immunology*
*Campbelltown Hospital*
*NSW, Australia*
[†] *Department of Respiratory Medicine*
*Campbelltown Hospital*
*NSW, Australia*
[‡] *Western Sydney University*
*Campbelltown Hospital*
*NSW, Australia*
alex.stoyanov@health.nsw.gov.au

## References

1. Tregoning JS, Flight KE, Higham SL, Wang Z, Pierce BF. Progress of the COVID-19 vaccine effort: viruses, vaccines and variants versus efficacy, effectiveness and escape. *Nat Rev Immunol*. 2021;21(10):626–636.
2. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Eng J Med*. 2021;384(22):2092–2101.
3. Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA vaccines. *Circulation*. 2021;144(6):471–484.
4. Bianchi L, Biondi F, Hansel K, Murgia N, Tramontana M, Stingeni L. Skin tests in urticaria/angioedema and flushing to Pfizer-BioNTech SARS-CoV-2 vaccine: limits of intradermal testing. *Allergy*. 2021;76(8):2605–2607.
5. Watanabe S, Waseda Y, Takato H, et al. Influenza vaccine-induced interstitial lung disease. *Eur Respir J*. 2013;41(2):474–477.
6. Steinberg J, Thomas A, Iravani A. $^{18}$F-fluorodeoxyglucose PET/CT findings in a systemic inflammatory response syndrome after COVID-19 vaccine. *Lancet*. 2021;18(397(10279)):e9.
7. Sahin Tutak A, Söylemez F, Konuk HB, et al. A patient presenting with ARDS after COVID-19 vaccination: a COVID-19 case report. *J Infect Public Health*. 2021;14(10):1395–1397.
8. Blumenthal KG, Freeman EE, Saff RR, et al. Delayed large local reactions to mRNA-1273 vaccine against SARS-CoV-2. *N Eng J Med*. 2021;384(13):1273–1277.
9. McMahon DE, Amerson E, Rosenbach M, et al. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: a registry-based study of 414 cases. *J Am Acad Dermatol*. 2021;85(1):46–55.
10. Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and Th1 T cell responses. *Nature*. 2020;586(7830):594–599.